2) Claims 1, 5, 13, and 15 are rejected under 35 USC 102(b) as being anticipated by Gavrilenko et al. The Examiner states that "The abstract teaches that lysozyme is administered intratracheally to patients ages 60 to under 30. The lysozyme is administered both with and without carbenicillin."

Response:

Claims 1 and 5 have been modified to specifically indicate that the intratracheally instilled lysozyme is administered **to the lung**. The applicants contend that the change of wording now places these claims in condition for allowance for the reasons stated below.

Gavrilenko teaches the use of lysozyme to treat **chronic bronchitis, which is a disease of the upper airways, not the lung.** There is no mention of the use of lysozyme to treat the lung nor is there any intention to do so by the authors. Therefore, such treatment cannot be presumed to be anticipated by the reference.

As stated in In re Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987):

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.".

Furthermore, it cannot be presupposed from the studies of Gavrilenko that lysozyme might even be useful for the purpose of treating a lung disorder. A necessary step to teach the utility of such treatment must include a demonstration of the actual penetration of intratracheally administered lysozyme into the lung as shown in the current application.

upper airways as shown by Gavrilenko. Such penetration of the lung by aerosolized lysozyme is predicated on the use of a sufficient amount of lysozyme (based on concentration and time interval of nebulization) to achieve detectable amounts in the pulmonary alveolar compartment. It is also dependent on generating a sufficiently small particle size in the nebulizer to facilitate penetration of the lysozyme into the deep lung. Determination of these parameters would require undue experimentation by one skilled in the art and cannot be presumed to be anticipated by the cited reference.

Gavrilenko et al. also fails to anticipate the need to determine the safety of intratracheal delivery of lysozyme to the lung (as shown in the current application). Since lysozyme is antigenic, examination of lung tissues is required to rule out the possibility of pulmonary inflammation. Such studies were never performed by Gavrilenko et al. Thus, the reference does not establish the safety (and, therefore, the potential benefit) of intratracheally instilling lysozyme into the lung.

Since the practicality and utility of intratracheally administering lysozyme to the lung rest entirely on determining the feasibility and safety of delivering lysozyme to the lung (which would require undue experimentation by one skilled in the art) the applicants' claims are neither obvious nor anticipated in the work of Gavrilenko et al.

As stated in In re The King v. Uhlemann Optical Co. 15 C.P.R. 99 (S.C.C. 1951)

"Whatever is essential to the invention or necessary or material for its practical working and real utility must be found substantially in the prior publication."

"... The requirements that must be met before an invention should be held to have been anticipated by a prior publication have been discussed in many cases and may be stated briefly. The information as to the alleged invention given by the prior publication must, for the purposes of practical utility, be equal to that given by the subsequent patent. Whatever is essential to the invention or necessary or material for its practical working and real utility must be found substantially in the prior publication. It is not enough to prove that an apparatus described in it could have been used to produce a particular result. There must be clear directions so to use it."

3) Claims 1-3 are rejected under 35 USC 102(b) as being anticipated by Kats et al. The Examiner states that "Kats teaches that lysozyme is administered by spraying it into the pharynx and larynx. It also teaches that it is derived from eggs."

Response:

As with Gavrilenko et al., Kats et al. only teach the use of lysozyme for the treatment of upper airway disorders involving the larynx and pharynx. There is no mention of the use of lysozyme to treat the lung. To demonstrate the effectiveness of lysozyme in treating the lung would require undue experimentation by one skilled in the art, as described above. Therefore, treatment of the lung with lysozyme is neither obvious nor anticipated from the work of Kats et al. The above-mentioned court decisions regarding prior references pertain to Kats et al.

4) Claims 1 and 2 are rejected under 35 USC 102(b) as being anticipated by [illegible] administered to patients by

Response:

As with Gavrilenko et al. and Kats et al., Zhorov et al. teach the use of lysozyme to treat an upper respiratory disorder; namely, post-intubation complications. No mention is made of treating the lung, nor is such treatment either obvious or anticipated from their work. To demonstrate the effectiveness of lysozyme in treating the lung would require undue experimentation by one skilled in the art, as described above. The above-mentioned court decisions regarding prior references pertain to Zhorov et al.

5) Claims 1-16 are rejected under 35 USC 103(a) as being unpatentable over Vyrenkov et al. taken with Gavrilenko et al., Zhorov et al., and Kats et al.

The Examiner states that "Vyrenkov teaches that patients with pneumonia were given lysozyme. The reference does not teach that the lysozyme was administered intratracheally, nebulized, that the lysozyme comes from eggs, or produced by fermentation, that it is given to a human neonate or that it is given in the specific amount in claim 16. The teachings of the other references are above."

"It would have been obvious to one of skill in the art to administer the lysozyme intratracheally since the other references establish that this is preferred way to administer the lysozyme to a patient. Further, since one wants to treat pneumonia one would administer it by nebulization. To derive the enzyme from eggs is known as evidenced by the references and if one gets the enzyme from fermentation it is also obvious since microorganisms routinely produce lysozyme. It is simply the choice of the artisan in an effort to optimize the results to use those different sources of the enzyme or administration of the enzyme. The

amount. To give the enzyme to a human neonate is simply the choice of the artisan. Infants contract pneumonia just like adults do. In fact, they contract it more thus one would want to definitely administer this to an infant. To use the lysozyme at the claimed amounts is also obvious since the amount is simply the choice of the artisan in an effort to optimize the claimed results. Further, the range 10 μg to 1 mg is a very broad range for such administration."

Response:

The Examiner applies a combination of references (Vyrenkov et al. taken with Gavrilenko et al., Zhorov et al., and Kats et al.) to reject claims 1-16. He argues that although Vyrenkov does not teach the use of intratracheally administered lysozyme to treat pneumonia, such use would be obvious to one skilled in the art, if combined with the other references, which establish intratracheal use as a "preferred" route of administration. **Nevertheless, it is the contention of the applicants that such references cannot be combined because they employ different approaches and rationales for the administration of lysozyme to patients and therefore teach away from one another. Vyrenkov teaches the use of endolymphatically administered lysozyme to stimulate the immune system as an effective method of treating pneumonia.** Endolymphatic administration may, in fact, be superior to intratracheal administration as a means of stimulating the immune system. It cannot be concluded from his work that intratracheal administration of lysozyme is the preferred route for stimulating the immune response in the treatment of pneumonia. Furthermore, the other references (Gavrilenko et al., Zhorov et al., Kats et al.) suggest a direct antibacterial effect of lysozyme and do not teach that intratracheal administration of lysozyme is useful for stimulating the immune system, either as a defense against pneumonia or any other respiratory disorder. **Indeed, under certain circumstances, intratracheal administration of lysozyme may be less effective than endolymphatic administration for treating pneumonia since such treatment may require stimulation of the immune system a.**

suggested by Vyrenkov et al. Thus, Vyrenkov et al. teaches away from the other cited references and from the claims of the current application.

As stated in In re Sernaker, 217 USPQ 1, 6 (CAFC 1983):

"Prior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings."

Further, as stated in Ex parte Levengood, 28 USPQ2d 1300 (PTOBA&I 1993):

"Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either of the prior art, or knowledge generally available to one of ordinary skill in the art, that 'would lead' that individual 'to combine the relevant teachings of the references.' ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done."

Further, as stated in In re The General Tire & Rubber Company v. The Firestone Type and Rubber Company Limited and Others R.P.C. 457 (1972)

"...it is not permissible to combine earlier unconnected publications to show anticipation, for, if combination of earlier unconnected publications is necessary to assemble all the elements of the invention said to have been anticipated. it follows that no one man has previously made the invention

Therefore, the statement by the Examiner that "It would have been obvious to one of skill in the art to administer the lysozyme intratracheally since the other references establish that this is preferred way to administer the lysozyme to a patient" is not warranted. Such a conclusion can only be based on undue additional experimentation by one skilled in the art to establish that intratracheal instillation of lysozyme produces the same effects on the immune system as endolymphatic administration. Further experimentation would also be needed to determine the safety of intratracheal delivery of lysozyme to the lung before this method is designated as the "preferred" route of administration.

The additional comments of the Examiner regarding the obviousness of 1) using microorganisms as a source of the lysozyme to treat pneumonia and 2) the administration of lysozyme to neonates to treat pneumonia are based on his contention that the combined references teach the treatment of pneumonia by intratracheal administration of lysozyme. This is clearly not the case as indicated above.

Concerning the claimed dosage range of lysozyme (10 μg to 1 mg), the applicants contend that this is entirely appropriate considering the differences in weight between neonates and adults, as well as possible variations in dosage based on the type and severity of pneumonia.

CONCLUDING REMARKS

Since the prior references cited by the Examiner, either separately or in combination, do not anticipate the current claims, it is respectfully requested that these claims now be placed in condition for allowance. Where appropriate, the

claims in order to place them in such condition. If the Examiner maintains his rejection to the current claims, it is respectfully requested that he provide an explanation of his reasoning in accordance with MPEP 706.02.

Very Respectfully,

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